

The rule of bigeminy revisited: analysis in sudden cardiac death syndrome

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Abstract

Background: The rule of bigeminy is commonly explained by a reentrant mechanism. We hypothesize that in patients with prolonged ventricular repolarization, the rule of bigeminy may be caused by premature ventricular complexes (PVCs) due to early afterdepolarizations. We evaluated these ventricular arrhythmias over extended periods in patients with sudden cardiac death syndrome. **Methods:** The electrocardiographic (ECG) characteristics of 15 recordings from the PhysioNet Sudden Cardiac Death Holter Database were analyzed for the persistence of bigeminy, interaction between the underlying cardiac rhythm and the coupling interval, and influence of a prolonged initiating RR cycle on the self-perpetuation of the arrhythmias.

Results: Eight (53%) patients had classic torsade de pointes (TdP), 5 (33%) had other polymorphic ventricular tachycardia (VT), and 2 (13%) had monomorphic VT. Group A, which comprised 6 of the patients with TdP, had the following ECG tetrad: (1) frequent ventricular bigeminy (>5% of total ventricular arrhythmias), (2) long corrected QT interval (>0.5 second), (3) relatively fixed coupling interval, and (4) onset of bigeminy ($n = 4$) and TdP ($n = 6$) after a short-long RR sequence. Patients in group A had slower heart rates (mean RR = 1.12 ± 0.26 vs 0.77 ± 0.13 seconds, $P < .01$), longer QT intervals (corrected QT = 0.57 ± 0.06 vs 0.45 ± 0.06 second; $P < .01$) and more cases with prominent U waves (83% vs 33%, $P < .05$) than patients in group B ($n = 9$), composed of patients who had other types of VT, or TdP without frequent bigeminy.

Conclusions: We identified a set of ECG characteristics that supports the notion that premature ventricular complexes during self-perpetuating ventricular bigeminy (“rule of bigeminy”) in long QT syndromes may be due to early afterdepolarizations.

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Ambulatory electrocardiogram; Early afterdepolarizations; Sudden cardiac death; Torsade de pointes; Ventricular bigeminy

Introduction

In classical cardiac electrophysiology much attention has been directed at characterizing patterns of frequent ventricular ectopic beat activity. Examples include descriptions of bigeminal rhythms in which there is an alternation between supraventricular and ectopic beats, trigeminy in which there is a sequence of 2 supraventricular beats and 1 ectopic beat, as well as many variants.^{1–9} Because frequent premature ventricular complexes (PVCs) often precede a sustained ventricular arrhythmia,^{10–17} researchers initially

hypothesized that drugs that suppressed ventricular ectopy would reduce the incidence of sudden cardiac death in high-risk patients. However, many classes of drugs, including those that suppress PVCs, have proarrhythmic effects.^{18–20} Furthermore, the analysis of the patterns of ectopy has not provided useful or consistent markers of risk.

We have hypothesized that the computer-assisted analysis of electrocardiographic (ECG) data over long time intervals offers the possibility of revealing dynamic signatures of arrhythmia that may have mechanistic and prognostic implications.⁹ One impediment to analyses of ECG records over long times has been the limited availability of such records. The posting of the PhysioNet Sudden Cardiac Death Holter Database offers an open access repository of data from patients who have a sustained

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Table 1
Clinical information and relevant ECG characteristics from patients (n = 15) of the PhysioNet Sudden Cardiac Death Database selected for the study

No.	Sex	Age (y)	Clinical history	Medication	Underlying cardiac rhythm	Mean NN (s)	QT interval (s)	QTc	PVCs				U waves	R-on-T	VT type
									Total (%)	Bigeminy (%)	Morphologies	CI (s)			
30	M	43	N/A	N/A	SR	0.67 ± 0.13	0.38 ± 0.03	0.43 ± 0.03	<1	3	2	0.43 ± 0.14	+	–	Polymorphic
31	F	72	HF	Digoxin; quinidine	SR	0.79 ± 0.05	0.44 ± 0.05	0.49 ± 0.05	6	1	2	0.61 ± 0.08	–	+	TdP
33 ^a	F	30	N/A	N/A	SR	1.33 ± 0.31	0.73 ± 0.07	0.66 ± 0.07	5	69	>2	0.58 ± 0.08	+	+	TdP ^a
34	M	34	N/A	N/A	SR	0.93 ± 0.12	0.40 ± 0.03	0.40 ± 0.02	<1	0	1	0.70 ± 0.27	+	+	Polymorphic
35	F	72	MVR	Digoxin	AF	0.90 ± 0.21	0.45 ± 0.03	0.52 ± 0.06	3	0	2	0.65 ± 0.10	–	+	Polymorphic
36	M	75	CS	Digoxin; quinidine	AF	0.95 ± 0.14	0.57 ± 0.05	0.53 ± 0.03	1	0	2	0.69 ± 0.09	+	–	TdP
37 ^a	F	89	N/A	N/A	AF	1.39 ± 0.19	0.69 ± 0.06	0.59 ± 0.06	1	6	1	0.74 ± 0.16	+	–	TdP ^a
41	M	N/A	N/A	N/A	SR	0.65 ± 0.05	0.36 ± 0.02	0.44 ± 0.02	7	0	1	0.37 ± 0.03	–	–	Polymorphic
44	M	N/A	N/A	N/A	SR	0.71 ± 0.07	0.50 ± 0.06	0.55 ± 0.06	10	45	2	0.56 ± 0.05	–	–	Monomorphic
45 ^a	M	68	VE	Digoxin; quinidine	SR	0.87 ± 0.06	0.61 ± 0.03	0.65 ± 0.04	1	30	2	0.65 ± 0.07	+	+	TdP ^a
46 ^a	F	N/A	N/A	N/A	SR	0.81 ± 0.17	0.46 ± 0.03	0.53 ± 0.03	14	80	>2	0.56 ± 0.06	–	+	TdP ^a
47 ^a	M	34	N/A	N/A	SR	0.99 ± 0.28	0.63 ± 0.13	0.63 ± 0.08	36	96	>2	0.55 ± 0.07	+	+	TdP ^a
48	M	80	N/A	N/A	SR	0.60 ± 0.15	0.39 ± 0.06	0.49 ± 0.07	3	0	1	0.54 ± 0.07	–	–	Monomorphic
50 ^a	F	68	CABG MVR	Digoxin; quinidine; propranolol; K ⁺ ; diuretics	AF	1.31 ± 0.31	0.78 ± 0.12	0.66 ± 0.09	5	10	>2	1.23 ± 0.58	+	+	TdP ^a
52	F	82	HF	N/A	SR	0.71 ± 0.05	0.34 ± 0.03	0.44 ± 0.04	13	38	1	0.34 ± 0.02	–	–	Polymorphic

Presence or absence of prominent U waves and R-on-T phenomenon is indicated by (+) and (–) respectively. Mean NN, QT interval, and QTc are reported as mean ± SD. N/A indicates data not available; SR, sinus rhythm; HF, heart failure; TdP, torsades de pointes; MVR, mitral valve replacement; AF, atrial fibrillation; CS, cardiac surgery (unspecified); VE, history of ventricular ectopy; CABG, coronary artery bypass graft.

^a Records with TdP that showed an ECG tetrad consistent with PVCs due to early afterdepolarizations (see text).

ventricular tachyarrhythmia leading to cardiac arrest.²¹ Although the clinical correlates in this retrospective collection are necessarily limited, the data provide a unique basis for initiating quantitative analyses and generating hypotheses for further testing.

In this study, we reassess ventricular bigeminy and other arrhythmias over extended time intervals in patients with sudden cardiac death syndrome. This analysis shows a subset of patients with torsade de pointes (TdP) whose Holter monitors reveal the constellation of frequent ventricular bigeminy, relatively fixed coupling intervals, prolonged ventricular repolarization, and onset of bigeminy after short-long RR sequences. This finding supports the notion that in this subset of patients, PVCs during ventricular bigeminy are due to early afterdepolarizations (EADs) and, hence, that the observation of persistent bigeminal rhythms may have prognostic value in selected clinical settings.

Methods

Patient population

We analyzed the 23 ambulatory ECG recordings that compose the open-access Sudden Cardiac Death Holter Database from PhysioNet²¹ (<http://www.physionet.org/physiobank/database/sddb/>). The recordings in this database were mainly obtained in the 1980s in Boston area hospitals and were later annotated and compiled as part of a study on ventricular arrhythmias. These records were analyzed with the methods described below. We selected a subset of 15 records without ventricular pacing, with documented sustained ventricular tachycardia (VT) or ventricular fibrillation (VF), and where beat labels provided could be visually corroborated. Table 1 shows the list of the selected patients and the main clinical characteristics.



Fig. 1. Representative ECG recordings from the PhysioNet Sudden Cardiac Death Holter Database. The first U waves of each trace are indicated by arrows, and the size of the grid interval is 0.2 second \times 0.5 mV. A, Patient 33 (group A). B, Patient 47 (group A). C, Patient 50 (group A). D, Patient 41 (group B). E, Patient 30 (group B).

Analysis techniques

The ECG recordings were displayed using the WAVE²¹ software package (available at <http://www.physionet.org>). Beat recognition was carried out using the *ann2rr* routine and was checked by a trained evaluator. The beat annotations are part of the data in the database. ECG characteristics, including underlying cardiac rhythm, presence of prominent U waves, and time of onset and type of VT were determined manually by a trained observer from records printed at a paper speed of 25 mm/s (Fig. 1). U waves were visually identified either as a second distinctive component of the T wave (T-U wave complex) (Fig. 1A), or as a consistent deflection occurring just after the end of the T wave (Fig. 1B, C, and E).

The corrected QT (QTc) interval ($QTc = QT/\sqrt{RR}$) was determined manually from time intervals during which there were no ventricular arrhythmias. Episodes of polymorphic VT that showed characteristic variation of the QRS axis in association with prolonged ventricular repolarization

($QTc > 0.44$ second) were classified as TdP.¹³ Heartprints and persistence plots, described below, were generated by using custom-written MATLAB (The MathWorks, Inc, Natick, Mass) software. After labeling ventricular beats (V) and supraventricular beats (N), ventricular arrhythmias were classified based on the composition of their repeating sequences: bigeminy (VN), trigeminy (VNN), quadrigeminy (VNNNN). We designate the number of intervening sinus beats between 2 consecutive V beats as the NIB value. We further identify concealed bigeminy (NIB values are all odd numbers), concealed trigeminy (NIB values are taken from the sequence 2, 5, 8, ...), and concealed quadrigeminy (NIB values are taken from the sequence 3, 7, 11, ...). A couplet is 2 consecutive V beats, and nonsustained VT is a sequence of 3 or more V beats that spontaneously terminates. PVCs that are not part of a couplet or nonsustained VT are called isolated. The coupling interval (CI) is the time duration from an N beat to a V beat as a function of NN interval.

Two new methods were used to give a visual display of the qualitative and quantitative features of the dynamics

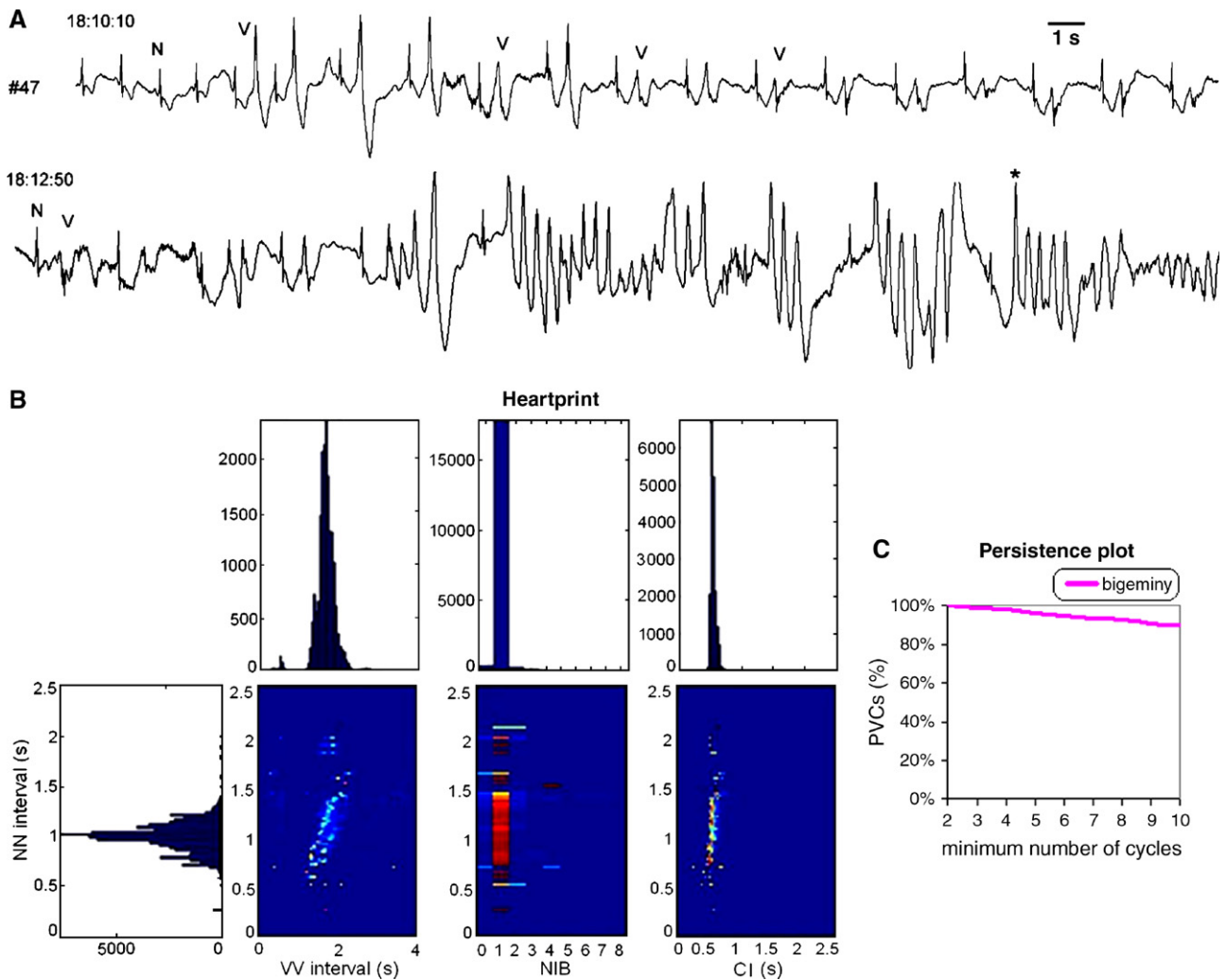


Fig. 2. Characteristics of record 47 (from group A). A, The ECG shows sinus rhythm and onset of persistent ventricular bigeminy after a long RR interval, with multiple PVC morphologies (supraventricular beat [N], ventricular beat [V]), followed by a complex sequence of couplets and nonsustained VT that leads to TdP (indicated by an asterisk). B, The heartprint, in which the redder colors represent more events, shows a large range of sinus rate (NN intervals varying in the range of 0.7 to 1.4 seconds), the time between 2 V beats (VV intervals) increases linearly with the sinus rate; the number of sinus intervening beats (NIB) between 2 V beats was mostly 1 for all sinus rates, and the coupling interval (CI) was relatively fixed for all sinus rates. C, The persistence plot shows that more than 90% of the PVCs occurred in bigeminal sequences that lasted for at least 10 repetitions of the sequence (VN).

over the entire 24-hour period: heartprints and persistence plots. A heartprint⁹ (see example in Fig. 2B) is a way to represent dependencies between the NN interval and (1) the ectopic beat interval (between 2 V beats, or VV interval), (2) NIB values, and (3) the CI. The ordinate of the 3 colored plots in the heartprint is the NN interval. The incidence of the VV intervals, NIB values, and the CI are indicated in the 3 colored plots, respectively, where the relative frequency of occurrence is indicated by the color (eg, red is associated with the highest incidence). The plots above the colored plots give the histograms of the VV intervals, the NIB values, and the CI, respectively. The histogram to the left of the colored plots gives the histogram of NN values. The persistence plots (see example in Fig. 2C) show the percentage of isolated PVCs involved in each ventricular rhythm as a function of the minimum number of repeating sequences required to identify a succession of RR intervals as belonging to that rhythm (in the example of Fig. 2C, the pink line indicates that more than 90% of the PVCs were involved in ventricular bigeminy of at least 10 repeating sequences of the basic sequence VN).

Statistical analysis

Ordinal variables are presented as mean \pm SD and categorical variables are expressed as percentage or number of samples in each category. Comparisons between ordinal variables were made by Student *t* tests, whereas categorical variables were compared by Barnard's exact tests. Statistical significance was established at the *P* less than .05 level.

Results

A summary of key ECG findings for all patients is given in Table 1. Eleven patients had sinus rhythm (73%) and 4 had atrial fibrillation (27%). Eight patients (53%) had classical TdP, 5 (33%) had other polymorphic VT, and 2 (13%) had monomorphic VT. For patients for whom drug therapy was available (*n* = 5), all were reportedly taking digoxin and 4 were reportedly taking quinidine. For further analysis, the records that showed frequent bigeminy and TdP (*n* = 6, indicated by asterisk in Table 1) are considered as group A, whereas records that did not have frequent

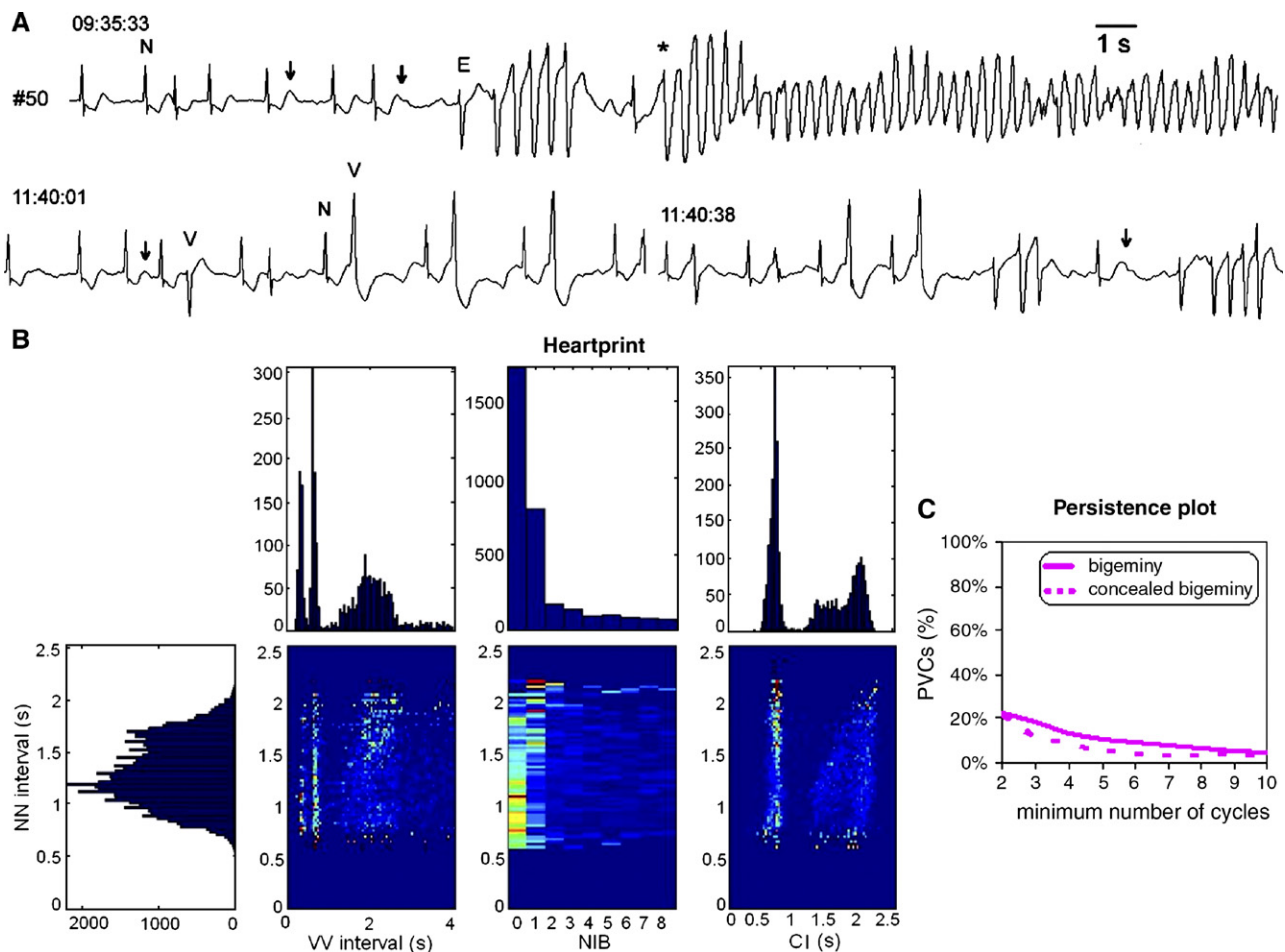


Fig. 3. Characteristics of record 50 (from group A). A, The ECG shows atrial fibrillation and onset of nonsustained VT after a ventricular escape beat (E). After another supraventricular beat, there is an initiation of TdP (indicated by an asterisk) that ended spontaneously after 50 seconds. Later, there were episodes of persistent ventricular bigeminy with multiple PVC morphologies that were initiated after a long RR interval. B, The heartprint shows the following characteristics: a large range of supraventricular rate (NN intervals varying in the range of 1 to 2 seconds); VV intervals were independent of the supraventricular rate; the NIB were mostly 0 or 1 for all supraventricular rates; and the CIs for PVCs were relatively fixed in the range of 0.5 to 0.6 second, whereas the CIs due to escape beats (CI values >1 second) were highly variable. C, The persistence plot shows that 10% of PVCs occurred in bigeminal sequences that lasted at least 5 repetitions of the basic sequence (VN), and also about 10% of PVCs occurred in a concealed bigeminal pattern that lasted at least 5 repetitions of odd NIB numbers.

bigeminy (n = 7) or that had frequent bigeminy but not TdP (n = 2) are group B (n = 9).

Group A subjects showed the following striking set of ECG features: (1) more than 5% of the isolated PVCs occurred during bigeminal rhythms consisting of at least 5 repetitions of the bigeminal rhythm, (2) a long QTc interval of more than 0.50 second, (3) a relatively fixed CI, and (4) the onset of the bigeminy after a preceding sequence of a short followed by a long RR interval. More importantly, in all the patients with the above characteristics we also found polymorphic ventricular tachycardia displaying the classic TdP morphology. Prominent U waves before the onset of bigeminy and/or TdP were present in 5 of them (83%).

We give 2 examples of group A. ECG excerpts and data analysis from 2 of the cases with this tetrad are shown in Figs. 1, 2, and 3. Figs. 1B and 2A (patient 47) show ECG excerpts revealing sinus rhythm, ST depression, and T-wave inversion. The QT interval was prolonged (QTc >0.60 second). After an episode of ventricular bigeminy with R-on-U phenomenon, an episode of sustained polymorphic VT with TdP morphology began at 18:12:50, which degenerated into VF. The heartprint (Fig. 2B) shows

that almost all PVCs occur as bigeminal rhythms with a sharply peaked CI of 0.55 second over a large range of sinus rates (NN intervals varying in the range 0.7 to 1.4 seconds). Furthermore, the persistence plot in Fig. 2C reveals that more than 90% of the isolated PVCs occur in bigeminal sequences of at least 10 repetitions. Notice that in the first excerpt in Fig. 2, the initial PVC is an interpolated beat. The record is consistent with TdP occurring in the presence of long QT intervals and bigeminy.

Figs. 1C and 3A (patient 50) shows the ECG of a patient with atrial fibrillation with a slow ventricular response (RR intervals varying in the range 1 to 2 seconds), ST-segment depression consistent with digoxin effect and a long QT interval (QTc >0.60 second) in the presence of quinidine. PVCs with different morphologies, ventricular escape beats, and frequent nonsustained VT are observed. After U waves of increasing amplitude (indicated by arrows in Fig. 3A) and a salvo of nonsustained VT, an episode of polymorphic ventricular tachycardia with TdP morphology started at 9:53:33 that ended spontaneously. The NIB plot of the heartprint (Fig. 3B) shows that most of the isolated PVCs occur in a bigeminal pattern. The occurrence of bigeminy during atrial fibrillation is similar to several cases of

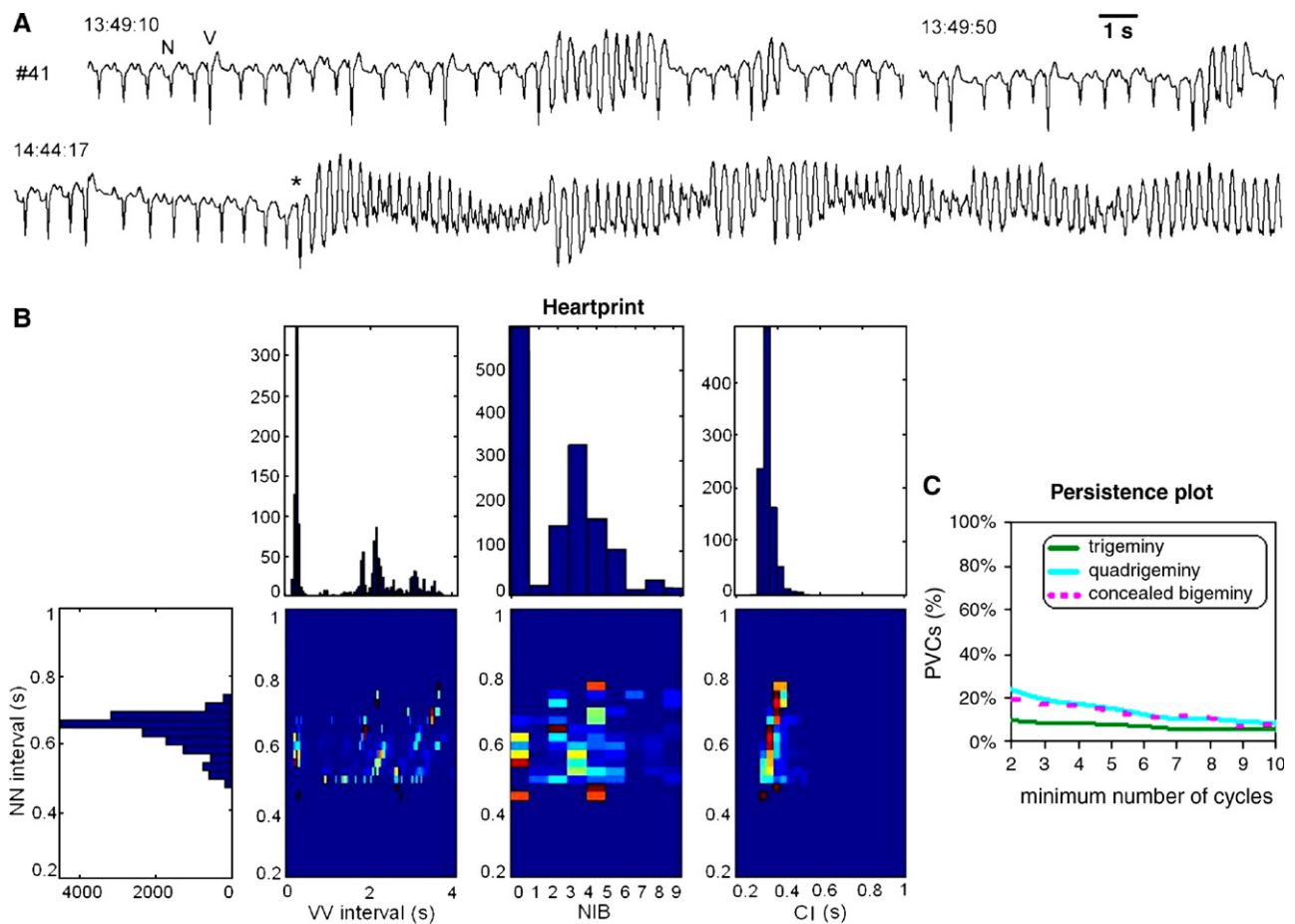


Fig. 4. Characteristics of record 41 (from group B). A, The ECG shows a sinus rhythm with concealed ventricular bigeminy with monomorphic PVCs, and 3 episodes of nonsustained VT. Later, a polymorphic VT (indicated by an asterisk) converted into VF (not shown). B, The heartprint shows the following characteristics: a low variability of the sinus rate (NN intervals varying in the range of 0.5 to 0.75 second); the VV intervals were independent of the sinus rate for values of VV intervals below 1 second and increased linearly with the sinus rate for values of VV above 1 second; and the CI was relatively fixed for all sinus rates. C, The persistence plot shows that quadrigeminy, trigeminy, and concealed bigeminy occurred for at least 10 repetitions of the basic sequence (VNNN, VNN, and odd NIB numbers, respectively). Each ventricular arrhythmia involved at least 10% of the PVCs.

bigeminy during atrial fibrillation initially reported by Pick et al.⁶ However, the CI plot of the heartprint shows that in addition to PVCs with a relatively fixed CI of 0.5 to 0.6 second over a range of RR intervals, there are very long CIs in the range of 1 to 2 seconds. These long CIs arise from ventricular escape beats after a long pause. These escape beats often immediately precede nonsustained VT episodes. In contrast to data from the patient in Fig. 2, the persistence plot in Fig. 3D shows that the overt bigeminal patterns do not persist for as long, and concealed bigeminal rhythms are also quite common. This record, similar to that in Fig. 2, is consistent with TdP in the presence of long QT intervals and bigeminy.

Next, we present 2 examples of group B subjects showing different characteristics based on the long-term quantitative analysis. Figs. 1D and 4A show the ECG of patient 41 with relatively fast sinus rhythm (NN interval in the range 0.5 to 0.75 second) and a normal QT interval (QTc = 0.44 second). In contrast to the heartprints in Figs. 2 and 3, the NIB plot in Fig. 4 shows that there is a range of different NIB values that fall into characteristic patterns as a function of the sinus rate. Thus, for sinus NN intervals

longer than 0.6 second, the NIB values tend to be odd numbers, consistent with concealed bigeminy, whereas for NN intervals between 0.5 and 0.6 second, there is a tendency to have quadrigeminy. The CI falls in the interval between 0.35 to 0.40 second over a broad range of NN intervals. There are frequent episodes of nonsustained VT, and an episode of polymorphic ventricular tachycardia that started at 14:44:17. In contrast to the 2 examples described from group A, patient 41 had virtually no bigeminal sequences, but there were frequent episodes of trigeminy, quadrigeminy, and concealed bigeminy that were persistent for more than 10 cycles (Fig. 4C). The onset of VT was not preceded by a short-long RR sequence. Despite the polymorphic VT, the fast heart rate, normal QT interval, and absence of other characteristics related to EADs distinguish it from the examples from group A (Figs. 2 and 3).

Figs. 1E and 5A show the ECG of patient 30, with sinus rhythm (NN intervals in the range of 0.4 to 1.1 seconds) and a normal QT interval (QTc = 0.43 second). The patient had PVCs with 2 morphologies. There was an episode of polymorphic VT that degenerated into VF. After resuscitation,

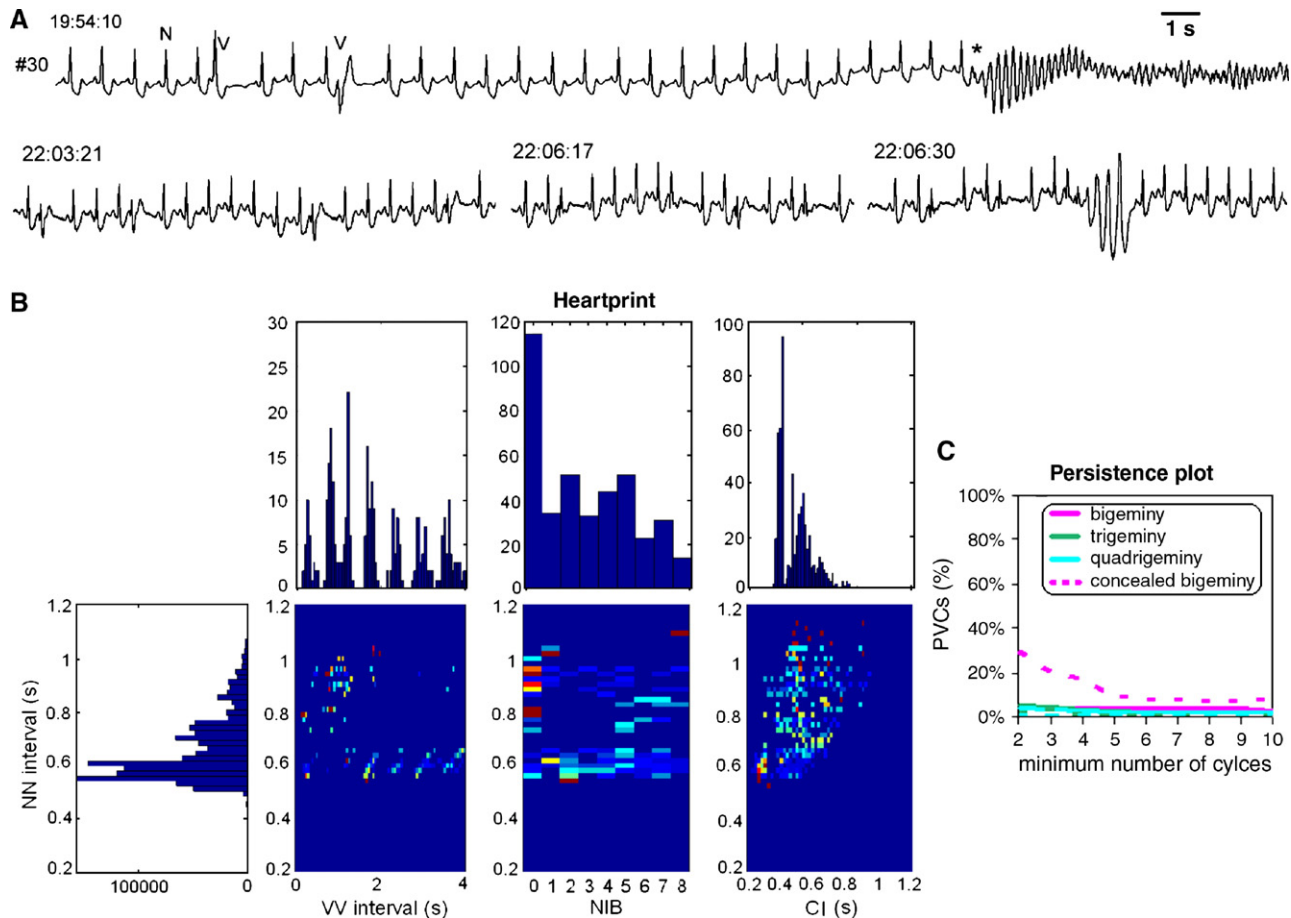


Fig. 5. Characteristics of record 30 (from group B). A, The ECG shows sinus rhythm with 2 morphologies of PVCs, a polymorphic VT (indicated by an asterisk) that converted into VF. After resuscitation, there was sinus rhythm with accelerated heart rate, PVCs, and 1 episode of nonsustained VT. B, The heartprint shows the following characteristics: a large range of sinus rates (NN intervals varying in the range of 0.4 to 1.1 seconds); the VV intervals were independent of the sinus rate for values of VV intervals below 1 second and increased linearly with the sinus rate for values of VV above 1 second; the NIB values depended on the sinus rate; and the CI was variable. C, The persistence plot shows that bigeminy, trigeminy and quadrigeminy, trigeminy, and concealed bigeminy were not persistent for more than 5 repetitions of the basic sequence (VN, VNN, VNNN, and odd NIB numbers, respectively). Episodes of 5 or more repetitions of each ventricular arrhythmia involved less than 5% of the PVCs.

Table 2

Characteristics of records from patients with TdP and frequent ventricular bigeminy (group A) compared with records from patients with other forms of VT, or TdP without frequent bigeminy (group B)

	Group A (n = 6)	Group B (n = 9)	P ^a
Age (y)	58 ± 25	65 ± 19	NS
Female	67% (4)	33% (3)	NS
Mean NN (s)	1.12 ± 0.26	0.77 ± 0.13	<.01
QT (s)	0.60 ± 0.12	0.40 ± 0.08	<.01
QTc (s)	0.57 ± 0.06	0.45 ± 0.06	<.01
CI (s)	0.72 ± 0.26	0.54 ± 0.14	NS
Prominent U waves	83% (5)	33% (3)	<.05
R-on-T phenomenon	83% (5)	33% (3)	<.05
Atrial fibrillation	33% (2)	22% (2)	NS
Multiform PVCs	83% (5)	56% (5)	NS

NS indicates non significant.

^a Continuous variables (presented as mean ± standard deviation) were compared by Student *t* tests, whereas discrete variables were compared by Barnard's exact tests. Discrete variables are presented as percentage (number of samples).

there was sinus rhythm with accelerated heart rate, isolated PVCs, and one episode of nonsustained VT. The NIB plot in Fig. 5B also shows that there was a range of different NIB values that fall into characteristic patterns as a function of

the sinus rate. In this case, for sinus NN intervals longer than 0.7 second, most of the NIB values are equal to 0, whereas NIB values greater than 0 occurred mostly at NN intervals less than 0.7 second. The CI is highly variable for NN intervals greater than 0.7 second, whereas for NN intervals less than 0.7 second there were mostly shorter and less variable CIs. Patient 30 had a few episodes of bigeminy, trigeminy, and quadrigeminy that involved less than 5% of the PVCs (Fig. 5C). Concealed bigeminy was more frequent, but it was not persistent for more than 5 cycles of the basic sequence (odd NIB numbers). The onset of VT was not preceded by a short-long RR sequence. Despite the presence of apparent U waves, the polymorphic VT that converted rapidly into VF, the fast heart rate, and the normal QT interval also distinguish this record from the examples from group A (Figs. 2 and 3).

Table 2 shows comparisons between groups A and B. Patients of group A had slower heart rate, considerably longer QT intervals, and more consistent presence of prominent U waves and VT initiation by R-on-T phenomena than patients of group B.

Fig. 6 shows that the onset of bigeminy was preceded by short-long RR sequences in 4 of 6 patients of group A

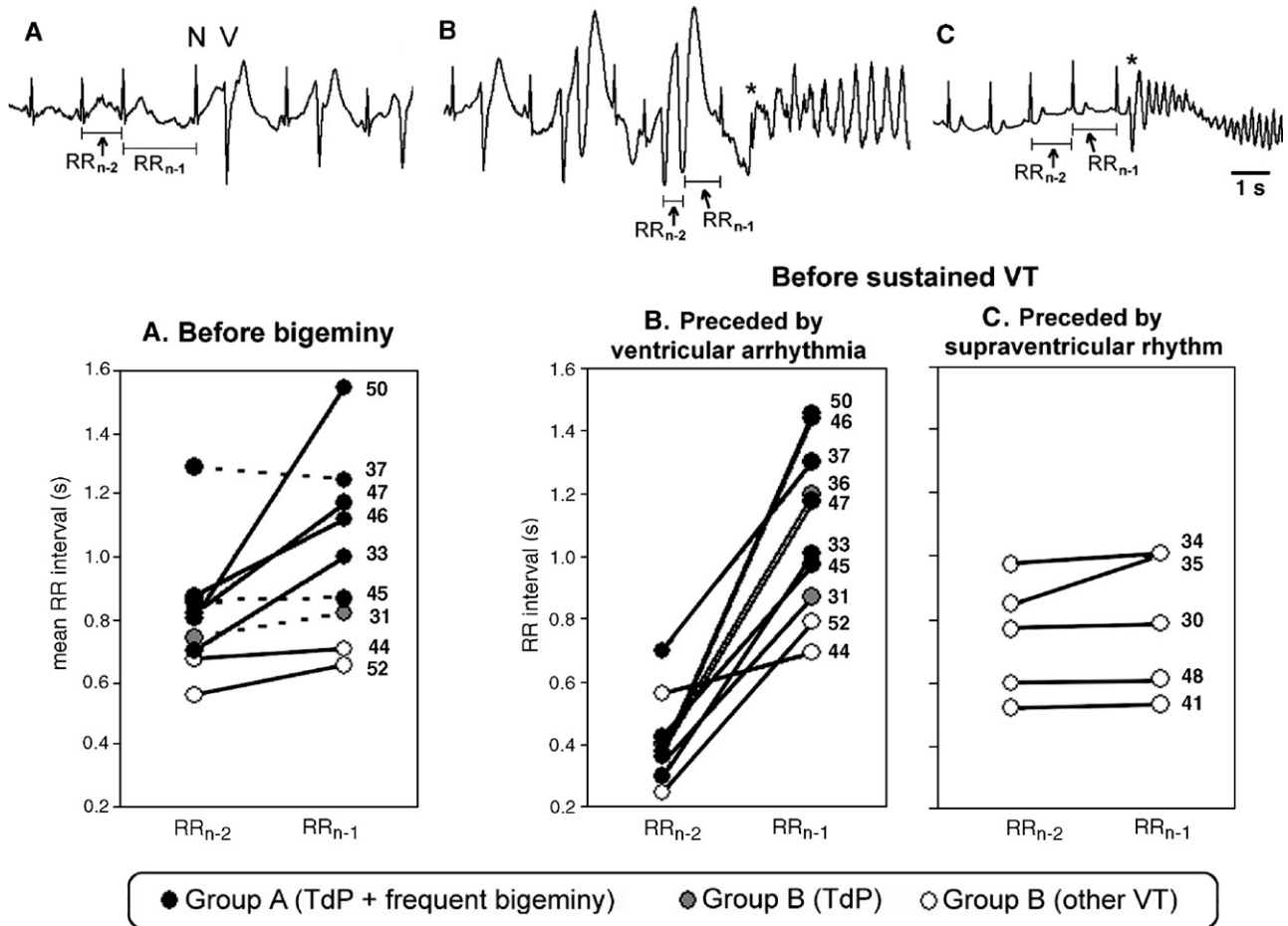


Fig. 6. ECG samples (top) and measured values (bottom) of RR intervals preceding the onset of bigeminy and sustained VT (indicated by an asterisk). The record number is indicated next to each corresponding data point. The onset of bigeminy was preceded by short-long RR sequences in 4 of 6 patients from group A (solid lines indicate a significant *P* value for a paired *t* test between the RR intervals preceding all the episodes of bigeminy in each patient). All patients with TdP had onset of sustained VT preceded by a short long RR sequence. All patients with onset of bigeminy after short-long RR sequences had also initiation of VT after a RR short-long sequence.

(solid lines indicate a significant *P* value of a paired *t* test between the RR intervals preceding all the episodes of bigeminy in each patient). All patients with TdP had onset of sustained VT preceded by a short-long RR sequence. Moreover, all patients with onset of bigeminy after short-long RR sequences had also initiation of VT after a short-long RR sequence, including 2 patients with VT different than TdP.

Discussion

In this study, we analyze complex patterns of ectopy based on Holter recordings. The findings lead us to reconsider certain classic approaches to the analysis of ventricular arrhythmia. In the original description of the “rule of bigeminy,” Langendorf et al⁶ hypothesized that the perpetuation of bigeminy might be due to a reentrant mechanism. During normal sinus rhythm there would be bidirectional conduction in a reentrant pathway. However, after a long RR interval, conduction would be facilitated in one direction leading to a PVC as a consequence of unidirectional block in the reentrant path. The following long interval due to the compensatory pause after the PVC would facilitate the maintenance of the unidirectional block after the next sinus beat and, thus, perpetuation of the bigeminal rhythm. Langendorf and Pick⁵ also proposed that in some instances, bigeminy could arise from interaction of the sinus rhythm with an independent parasystolic focus, a viewpoint that was confirmed and extended by Jalife and colleagues.^{2,3} Subsequently, Cranefield²² hypothesized that the formation of ventricular EADs could be facilitated after a long RR interval, thereby leading to a PVC. Here also the following compensatory pause would facilitate a subsequent EAD and perpetuation of the bigeminal rhythm. Thus, there are at least 3 different mechanisms that could lead to qualitatively similar rhythms in ECG records, and it is likely that all 3 mechanisms are important in the generation of arrhythmia in selected patients.

Previous retrospective studies of sudden cardiac death based on Holter monitor analyses show great variability among the records of the individual patients, and the current series is no exception.^{10,11,14-17,23-25} These previous studies have identified a variety of ECG characteristics immediately preceding the onset of ventricular tachyarrhythmias and sudden cardiac death including accelerated sinus rate,^{11,14,16} increased number and complexity of PVCs,^{11,14,23} R-on-T phenomenon,^{11,14} transient bradycardia,¹⁴ and short-long R-R interval sequences.^{14,16,24} Moreover, in patients with acquired prolonged repolarization, TdP has been observed in association with underlying bradycardia,^{11,16,25} increase of heart rate in the minute immediately before the tachyarrhythmia,¹⁶ “cascade phenomenon” (short-long RR sequences with a progressive increment in the complexity of the ventricular arrhythmias),^{16,24} sometimes with increased QT prolongation,²⁵ and prominent U waves.^{17,26} Notably, bigeminal rhythms have been identified immediately preceding sudden cardiac death in patients with acquired or congenital QT prolongation.^{13,16,17,24} However, none of the earlier studies systematically analyzed the patterns of

complex ectopy over long times. Furthermore, although it is clear that different mechanisms of PVCs may prevail in different patients, there is still little understanding about how to identify potential markers of mechanisms based on the surface ECG characteristics.

We observed the rule of bigeminy in patients of group A (*n* = 6) whose Holter records showed its onset after a long RR interval, a relatively fixed CI, perpetuation of the bigeminy to the exclusion of other rhythms over a range of sinus rates, and during atrial fibrillation (Table 1). These characteristics are more likely indicators of PVCs due to EADs than PVCs due to reentry or parasystole, especially when characteristic ECG features of long QT syndrome (long QT intervals, TdP, prominent U waves, and the R-on-T phenomenon) are concurrently observed.^{13,16,17,24-28} Because of the association of these ECG features with EADs, we believe that EADs provide a plausible mechanism for the arrhythmias in patients of group A. Among the records of the patients in group B (*n* = 9), the ECG characteristics are not consistent with an EAD mechanism, even for those 2 subjects that displayed bigeminy. For example, for the patient whose record is displayed in Fig. 4, there is polymorphic VT, fast heart rate, normal QT intervals, and frequent nonsustained VT. These findings suggest that in this patient, the ectopy may be associated with delayed afterdepolarizations and VT induced by increased catecholaminergic activity.²⁹ However, the unique distribution of NIB values associated with changes in the sinus rhythm revealed by the heartprint raise the alternative possibility that modulated parasystole could also be a potential mechanism for this record.^{1-3,30} The same mechanisms are likely to explain the other example from group B (Fig. 5), which shows polymorphic VT that started suddenly during normal sinus rhythm and normal QT intervals. The PVCs had highly variable CI before the onset of VT, but after resuscitation the PVCs occurred at a faster heart rate and showed more fixed CI.

These observations based on the data in the PhysioNet Sudden Cardiac Death Database are consistent with observations of the onset of TdP in patients with the acquired or congenital long QT syndrome^{13,16,17,24-27} and in canine models of the long QT syndrome.¹² In all of these circumstances, bigeminal rhythms often precede the onset of TdP, and EADs have been hypothesized as a potential mechanism to initiate TdP.^{12,13,17,24,28,31} The TdP is thought to be sustained as a reentrant spiral that exists in the absence of an anatomical barrier.^{12,31,32} However, this prior work did not elucidate the characteristics of the rhythms over long times and does not provide clear clues about the possible electrophysiologic manifestations of these rhythms well before the onset of tachycardia.

The incidence of the EAD mechanism is unknown because there is no ready way to define its presence clinically. EADs are likely most prevalent in acquired and congenital long QT syndromes.^{13,33} It is estimated that 1 in 10 000 individuals is a carrier of a long QT syndrome gene and that long QT syndrome causes 3000 to 4000 sudden deaths in children and young adults each year in the United States.¹³ It is estimated that less than 5% of the cases of

sudden cardiac death are due to arrhythmias associated with congenital and acquired long QT syndrome.³³ However, the mortality rates among patients with congenital long QT are very high, especially in young patients.²⁷

From a clinical perspective, the findings of the present study are of interest because they may allow automated identification of a subset of patients with high risk of TdP. Furthermore, the detection of sustained episodes of prolonged ventricular bigeminy (rule of bigeminy) over a wide range of supraventricular rates in the specific context of QT(U) prolongation is consistent with EADs as the underlying mechanism. Confirmation of this marker of electrical instability requires the analysis of longer recordings along with experimental data. Of note, this finding suggests the potential use of expanding conventional Holter analysis to include an assessment of the duration (not just the presence) of bigeminal episodes and their relationship to the underlying supraventricular cycle lengths. The induction of bigeminy by pharmacologic agents may also provide a marker of an important proarrhythmic effect even in the absence of TdP. The present study supports the view that ventricular bigeminy may be generated by many different mechanisms and suggests that longer-term recordings may provide hitherto unmined clues as to mechanism and prognosis beyond the very limited use of standard “beat counting” summaries.

The current work has identified characteristic features in patients with acquired long QT and frequent bigeminy based on Holter recordings that we propose may be associated with EADs. If this mechanism is confirmed in future studies, then it could have implications for therapy because the ectopic site(s) of the EADs could be target(s) for radiofrequency ablation. To date, the use of ablation in patients with long QT has been limited. Recently, Haïssaguerre et al³⁴ reported the successful mapping and ablation of arrhythmogenic foci in 7 patients with either long QT or Brugada syndromes and ventricular fibrillation. By targeting the sites of PVCs in the Purkinje fiber system or the right ventricular outflow tract, they successfully eliminated the recurrence of symptomatic ventricular arrhythmias. Earlier work reported on the surgical ablation of symptomatic ventricular bigeminy in a heterogeneous group of 18 patients.³⁵ However, because long QT was not documented in these patients and TdP was reported only in one case, there is no direct relevance to the current work.

Limitations

The current analysis is based on a retrospective database in which there is only partial information about clinical presentation and in which all the patients experienced sudden cardiac arrest. The number of patients in this database, however, is quite small. It is important to evaluate our findings on more extensive data, but we are not aware of other databases that are publicly available. Recordings from implantable cardiac defibrillators may provide a rich source of data for future analysis. However, the data from the implantable cardiac defibrillators would also be limited because the ECG record would not be generally available so that beat recognition would have to be inferred from the interbeat intervals. Furthermore, because the prevalence of

the bigeminal rhythms in patients not at risk for sudden death remains to be evaluated, the current analysis cannot be used to prospectively predict patients at risk for sudden cardiac death based on ECG records. Finally, the criterion used to evaluate the QT interval was based on the Bazett formula. This formula has a rate-dependence bias and consequently is not reliable, especially for heart rates slower than 60 beats per minute or faster than 100 beats per minute.^{36–38} However, in the current context, the QT interval was longer than 0.6 second in 5 of the 6 and longer than 0.5 second in all patients in Group A. These values would qualify for long QT using other contemporary criteria.

Conclusion

We have identified a tetrad of ECG characteristics: (1) frequent ventricular bigeminy (>5% of total ventricular arrhythmias), (2) very long QTc interval (>0.5 second), (3) relatively fixed CI, and (4) onset of bigeminy after a short-long RR sequence in a subset of patients (group A). These observations are consistent with the notion that PVCs during ventricular bigeminy in this subset of patients are due to EADs.

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